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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,138	ZELDIS, JEROME B.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11 and 14-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11 and 14-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/23/2008 and 2/12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 2/12/2008, are acknowledged and entered. Claims 12-13 have been cancelled by Applicant. Claims 10-11 and 14-24 are pending and under examination.

Upon further consideration and in view of new prior art cited by Applicants in the IDS filed 12/23/2008, the Examiner is herein newly rejecting the pending claims as being prima facie obvious over the cited prior art. In light of disclosures in the prior art that TNF-α and angiogenesis are implicated in idiopathic pulmonary fibrosis disease progression and thalidomide is suggested in the prior art to be useful in treating angiogenic and TNF-α related disorders, it would have been obvious to one skilled in the art to have used thalidomide to treat idiopathic pulmonary fibrosis (see the new rejection under 35 U.S.C. 103 below).

Response to Arguments

Any previous rejections and/or objections to claims 12-13 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed 12/23/2008 and 2/12/2009. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 12-13 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is **withdrawn** in light of Applicant's cancellation of claims 12 and 13.

The rejection of claims 10-24 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement regarding a "solvate" of thalidomide, is **withdrawn** in light of Applicant's amendments.

The rejection of claims 10-24 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is **withdrawn** in light of Applicant's arguments and evidence of therapeutic activity provided in post-filing art.

Claim Rejections - 35 USC § 103 – New Grounds of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-11 and 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over **D'Amato** (USP No. 5,593,990; Issued 1/14/1997) (Reference A65 in IDS filed 10/24/2006) and **Kaplan *et al.*** (WO 92/14455; Published Sept. 3, 1992) (newly cited) in view of **Keane *et al.*** (Am. J. Respir. Crit. Care Med., 2001, vol. 164, pages 2239-2242) (newly cited) and **Allen *et al.*** (Respir. Res., 2002, vol. 3, no. 13) (Reference C180 in IDS filed 12/23/2008).

The instant claims are drawn to treating idiopathic pulmonary fibrosis comprising administering to a patient having idiopathic pulmonary fibrosis a therapeutically effective amount of thalidomide.

D'Amato discloses methods of inhibiting angiogenesis and treating disease states resulting from angiogenesis comprising administering thalidomide (Abstract; col. 4, lines 58-67; col. 5, lines 15-22). Administration of thalidomide and related compounds include standard

routes of administration such as oral, topical, transdermal, or parenteral as recited in claim 19 (col. 12, lines 59-65). For oral administration to humans, D'Amato discloses doses of 0.1 to 300 mg/kg/day, most preferably 1 to 10 mg/kg/day (col. 13, lines 6-15). For an average human, the most preferable doses equate to approximately 70 to 700 mg/day, thus obviating the dose ranges recited in claims 14-18. With respect to claim 20, D'Amato discloses formulations such as capsules, cachets, or tablets (col. 13, lines 30-36).

Kaplan *et al.* disclose methods for controlling abnormal concentrations of TNFα in human tissues comprising administration of compounds of Structure (II), which include thalidomide when R" is H and X is C=O (Abstract; page 7, lines 2-22; Figure 1-3). Similar to D'Amato, Kaplan *et al.* disclose the administration of compounds of the invention (*e.g.*, thalidomide) in carriers such as tablets, pills, and lozenges (page 21, lines 1-11). With regard to claim 11, Kaplan *et al.* teach that a compound of the invention can be co-administered with another therapeutic agent effective to treat the condition associated with the debilitating effect (page 22, lines 9-23).

The instant claims differ from D'Amato and Kaplan *et al.* in that neither reference expressly discloses the treatment of idiopathic pulmonary fibrosis.

However, Keane *et al.* teach that the pathology of idiopathic pulmonary fibrosis features dysregulated and abnormal repair with exaggerated angiogenesis, fibroproliferation, and deposition of extracellular matrix, leading to progressive fibrosis and loss of lung function (page 2239, left column). Evidence of neovascularization and extensive vascular remodeling has been observed in patient with interstitial fibrosis and during the pathogenesis of pulmonary fibrosis in a rat model of bleomycin-induced pulmonary fibrosis (*id.*). The authors disclose that administration of the angiostatic chemokine IP-10 leads to a reduction in pulmonary fibrosis that is mediated through inhibition of angiogenesis in a murine model of pulmonary fibrosis. (page 2239, right column). In the current study, the authors demonstrate that the angiogenic CXC chemokine ENA-78 is elevated in idiopathic pulmonary fibrosis lung tissue and is associated with increased angiogenic activity (page 2241, left column).

Allen *et al.* teach that mice over-expressing TNF-α develop IPF-like fibrosis, whereas TNF-α-deficient or double TNF-α receptor knockout mice show resistance to bleomycin-

induced fibrosis (page 3, right column of PDF submitted by Applicants). The authors further teach that promising results have been obtained by treating IPF patients with pirfenidone, a novel antifibrotic agent with anti-TNF-α properties (*id.*).

In light of the above cited prior art, it would have been *prima facie* obvious to one of ordinary skill in the art the time the invention was made to have used thalidomide to treat idiopathic pulmonary fibrosis. The skilled artisan would have been motivated to do so because thalidomide is suggested in the prior art to not only inhibit angiogenesis and thus is useful in the treatment of angiogenic-related disease and disorders (D'Amato) but to also inhibit TNF-α and thus is useful in the treatment of diseases and disorders characterized by abnormal TNF-α concentrations (Kaplan *et al.*). As both angiogenesis and TNF-α are implicated in the pathogenesis of idiopathic pulmonary fibrosis as evidenced by Keane *et al.* and Allen *et al.*, the skilled artisan would have been imbued with at least a reasonable expectation that a compound that inhibits both angiogenesis and TNF-α would be an effective treatment for idiopathic pulmonary fibrosis.

Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over **D'Amato** (USP No. 5,593,990; Issued 1/14/1997) (Reference A65 in IDS filed 10/24/2006) and **Kaplan *et al.*** (WO 92/14455; Published Sept. 3, 1992) (newly cited) in view of **Keane *et al.*** (Am. J. Respir. Crit. Care Med., 2001, vol. 164, pages 2239-2242) (newly cited) and **Allen *et al.*** (Respir. Res., 2002, vol. 3, no. 13) (Reference C180 in IDS filed 12/23/2008) as applied to claims 10-11 and 14-20 above, and further in view of **Selman *et al.*** (Chest, 1998, vol. 114, pages 507-512) (newly cited).

Claims 21-24 differ from D'Amato, Kaplan *et al.*, Keane *et al.*, and Allen *et al.* in that the references do not teach the doses of the second active agent recited in claims 21-24.

However, Selman *et al.* teach combination therapy for the treatment of idiopathic pulmonary fibrosis comprising administration of prednisone at a dose of 1.0 mg/kg/day (about 70 mg/day for an average human patient) for 1 month followed by biweekly taper to a dose of 15 mg/day; colchicine at a daily dose of 1.0 mg; and D-penicillamine at a dose of 600 mg/day (Abstract). As such, the doses of second active agent recited in claims 21-24 would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made. For example, if the skilled artisan desired to treat idiopathic pulmonary fibrosis with a combination of thalidomide and prednisone, which has been used to treat idiopathic pulmonary fibrosis as evidenced by Allen *et al.*, a dose of 70 mg/day prednisone would have been an obvious starting dose because such a dose has previously been administered to patients having idiopathic pulmonary fibrosis.

Claims 10-11 and 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Banerjee *et al.*** (US 2004/0131614 A1; Published Jul. 8, 2004; Filed Jul. 18, 2003) (newly cited) in view of **Kaplan *et al.*** (WO 92/14455; Published Sept. 3, 1992).

Banerjee *et al.* disclose methods of treating pulmonary disorders comprising administering TNFα inhibitors, including TNFα antibodies (Abstract; page 2, [0014])). Such pulmonary disorders include idiopathic pulmonary fibrosis as recited in the instant claims (page 1, [0006]; page 2, [0014]-[0016]; page 12, [0102]-[0104]). With regard to combination therapy as recited in claim 11, Banerjee *et al.* disclose that the TNFα antibody is administered with at least one additional therapeutic agent (page 2, [0018]). Doses of the disclosed anti-TNFα antibodies for administration to a patient having a pulmonary disorder range from 10-150 mg, more preferably 20-80 mg, and most preferably 40 mg, thus obviating the doses recited in claims 21-24 (page 14, [0127]). With regard to additional therapeutic agents suitable for combination with the disclosed anti-TNFα antibodies, thalidomide as recited in the instant claims is one such therapeutic agent contemplated for combination with the treatment methods disclosed in Banerjee *et al.* (page 16, [0137]).

As further motivation to administer thalidomide in combination with an anti-TNFα antibody disclosed in Banerjee *et al.* for the treatment of idiopathic pulmonary fibrosis, the Examiner refers to Kaplan *et al.*, who disclose methods for controlling abnormal concentrations of TNFα in human tissues comprising administration of compounds of Structure (II), which include thalidomide when R" is H and X is C=O (Abstract; page 7, lines 2-22; Figure 1-3). Kaplan *et al.* disclose the administration of compounds of the invention (*e.g.*, thalidomide) in carriers such as tablets, pills, and lozenges (page 21, lines 1-11). With regard to claim 11,

Kaplan *et al.* teach that a compound of the invention can be co-administered with another therapeutic agent effective to treat the condition associated with the debilitating effect (page 22, lines 9-23).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered a combination of an anti-TNFα antibody disclosed in Banerjee *et al.* and thalidomide as disclosed in both Banerjee *et al.* and Kaplan *et al.* for the treatment of idiopathic pulmonary fibrosis. The skilled artisan would have been motivated to do so because Banerjee *et al.* teach that idiopathic pulmonary fibrosis is a disease associated with abnormal TNFα levels and thus provide a method for treating idiopathic pulmonary fibrosis comprising administration of an anti-TNFα antibody alone, or on combination with another therapeutic agent such as thalidomide. Kaplan *et al.* provide further motivation to select thalidomide for the combination therapy disclosed in Banerjee *et al.* wherein they disclose that thalidomide and related compounds are useful for treating diseases characterized by abnormal TNFα levels both alone and in combination with additional therapeutic agents.

In view of the above cited prior art, the skilled artisan would have been imbued with at least a reasonable expectation that a combination of an anti-TNFα antibody and thalidomide would be effective for the treatment of idiopathic pulmonary fibrosis.

Claims 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Banerjee *et al.*** (US 2004/0131614 A1; Published Jul. 8, 2004; Filed Jul. 18, 2003) (newly cited) in view of **Kaplan *et al.*** (WO 92/14455; Published Sept. 3, 1992) as applied to claims 10-11 and 19-24 above, and further in view of **D'Amato** (USP No. 5,593,990; Issued 1/14/1997) (Reference A65 in IDS filed 10/24/2006).

Banerjee *et al.* and Kaplan *et al.* disclose as applied *supra* and are herein applied for the same teachings in their entirety. Claims 14-18 differ from Banerjee *et al.* and Kaplan *et al.* in that neither reference discloses the claimed doses of thalidomide.

However, D'Amato discloses administration of thalidomide and related compounds via standard routes of administration such as oral, topical, transdermal, or parenteral as recited in

claim 19 (col. 12, lines 59-65). For oral administration to humans, D'Amato discloses doses of 0.1 to 300 mg/kg/day, most preferably 1 to 10 mg/kg/day (col. 13, lines 6-15). For an average human, the most preferable doses equate to approximately 70 to 700 mg/day, thus obviating the dose ranges recited in claims 14-18.

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer thalidomide using the doses disclosed in D'Amato in combination with an anti-TNFα for the treatment of idiopathic pulmonary fibrosis as suggested and motivated by Banerjee *et al.* in view of Kaplan *et al.* The skilled artisan would have been imbued with at least a reasonable expectation that the doses disclosed in D'Amato would be effective for inhibiting TNFα as disclosed in Kaplan *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614